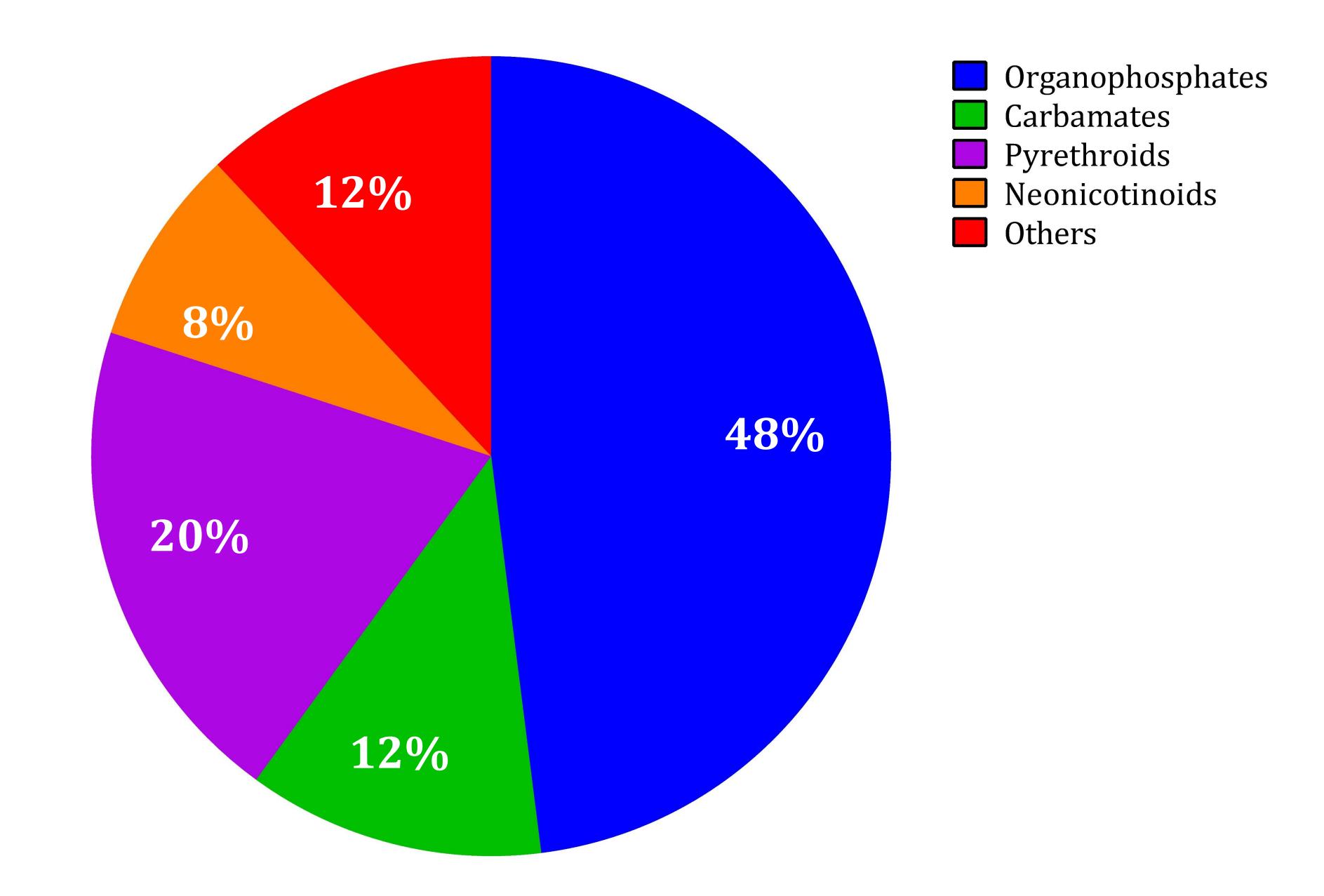


**Figure S1** | **Geographic location of the Study area.** The study area chosen was Vadapalanji Village Panchayat located near Madurai Kamaraj University in Madurai District, Tamilnadu State of India.

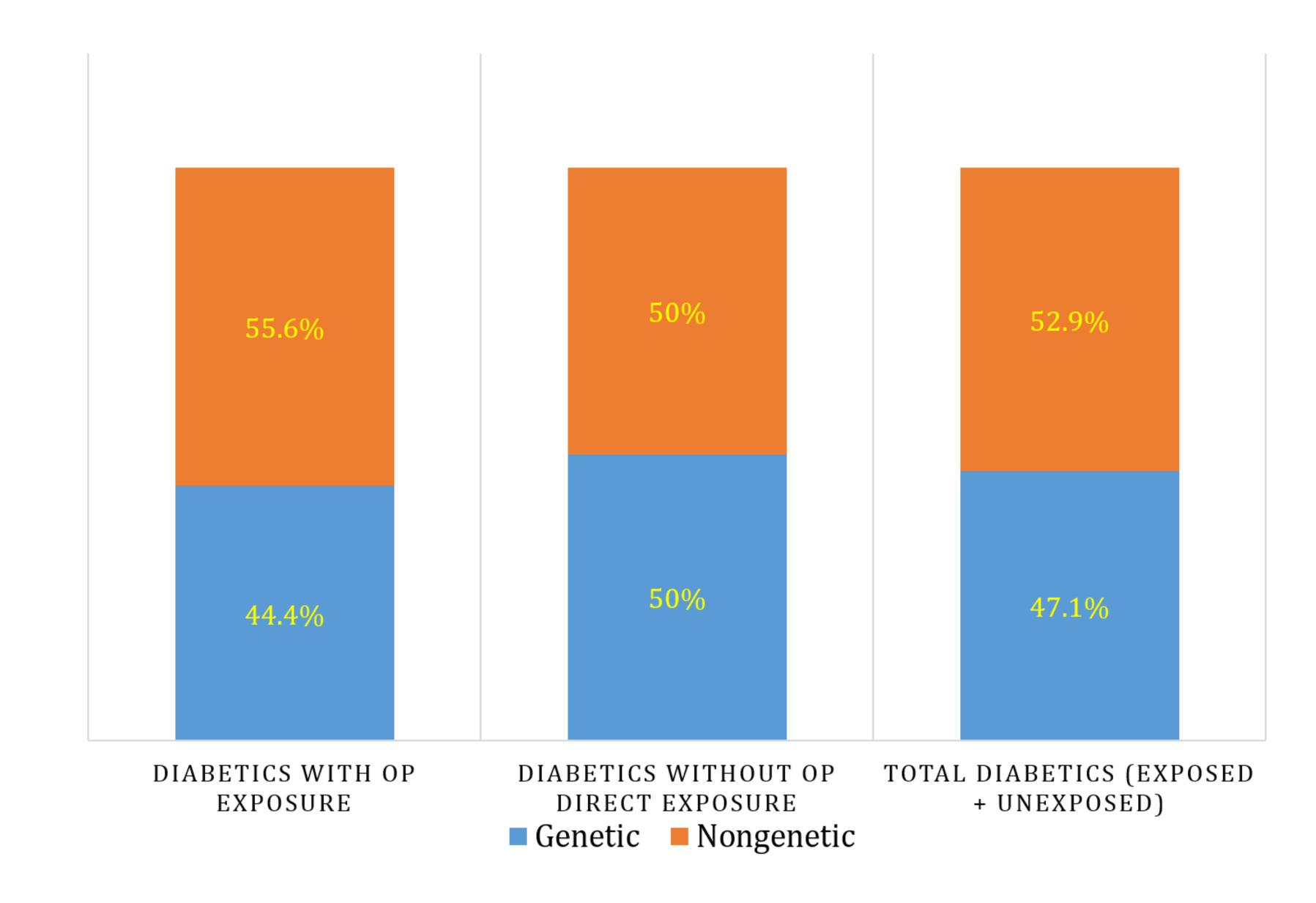




h

Total Number of Participants	3080
Number of participants directly exposed to OP	1686
Number of participants not directly exposed to OP	1394
Number of diabetic in exposed group	308
Number of diabetic in nonexposed group	86
Number of nondiabetic in exposed group	1378
Number of nondiabetic in nonexposed group	1308
Odds ratio (age and sex adjusted)	1.3995
95% Confidence interval	0.738, 2.471
z statistic	9.565
	P<0.0001





**Figure S2**| **Organophosphate exposure associates with diabetic prevalence**. Villagers around Madurai Kamaraj University were surveyed for exposure to organophosphates and diabetic prevalence. **a.** Frequency of usage of different types of insecticides in the study area. **b.** Characteristics of study population, odds ratio, 95% confidence interval and z statistic. **c.** Prevalence of genetic familial diabetic history among the diabetics with and without direct OP exposure (N=3080). The percentages of each group are mentioned within the slice of pie chart or bars.

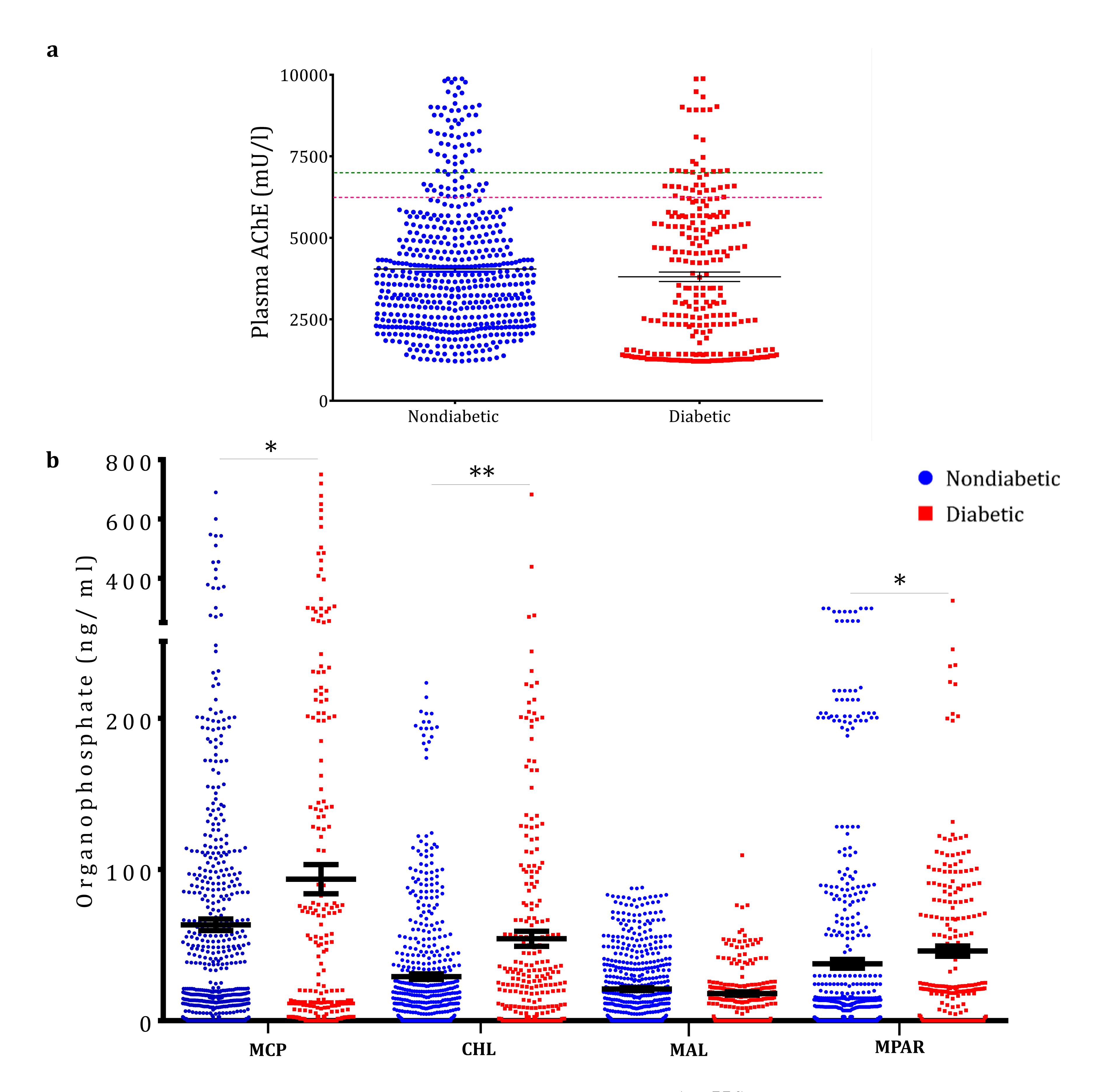
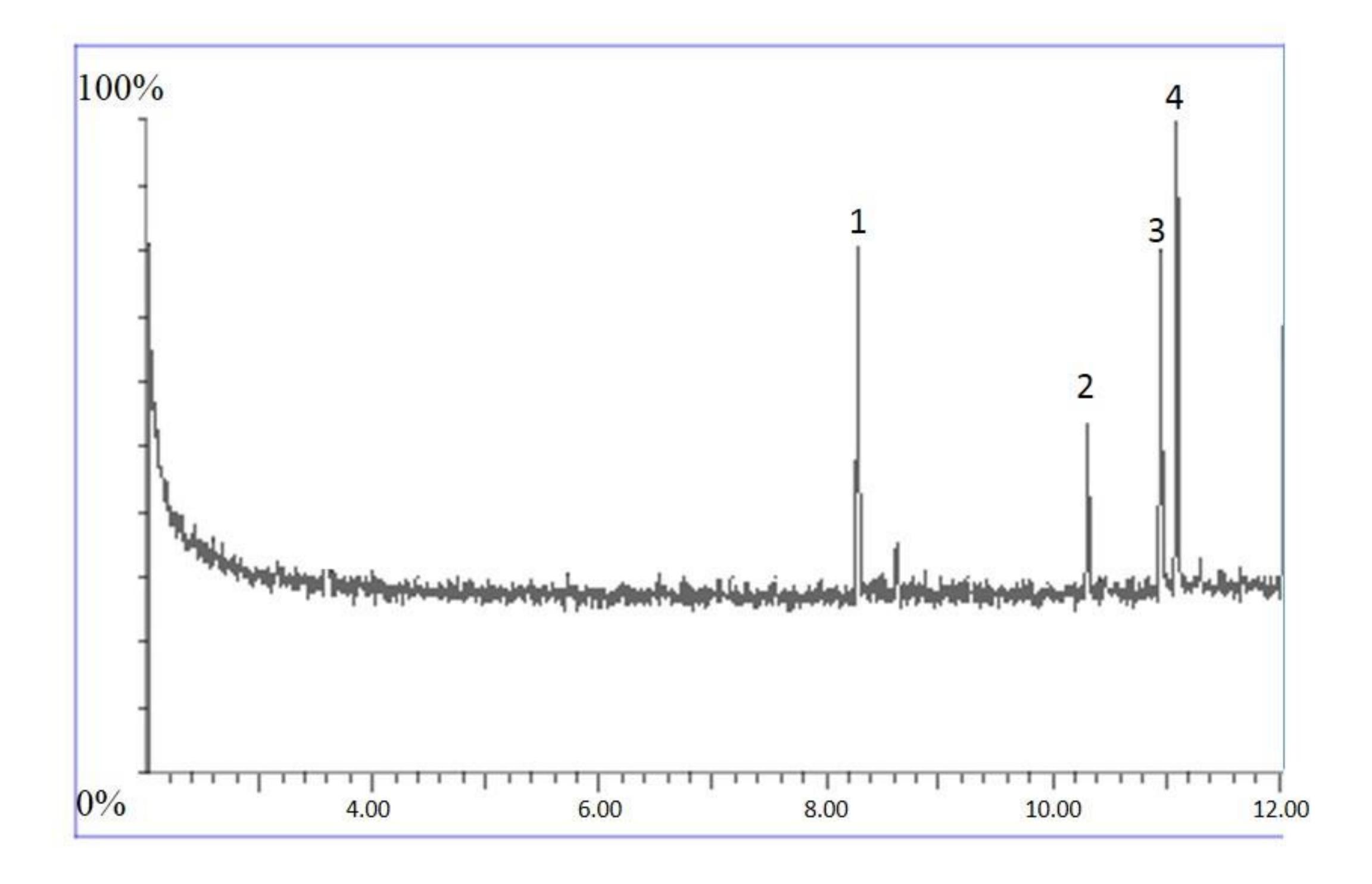


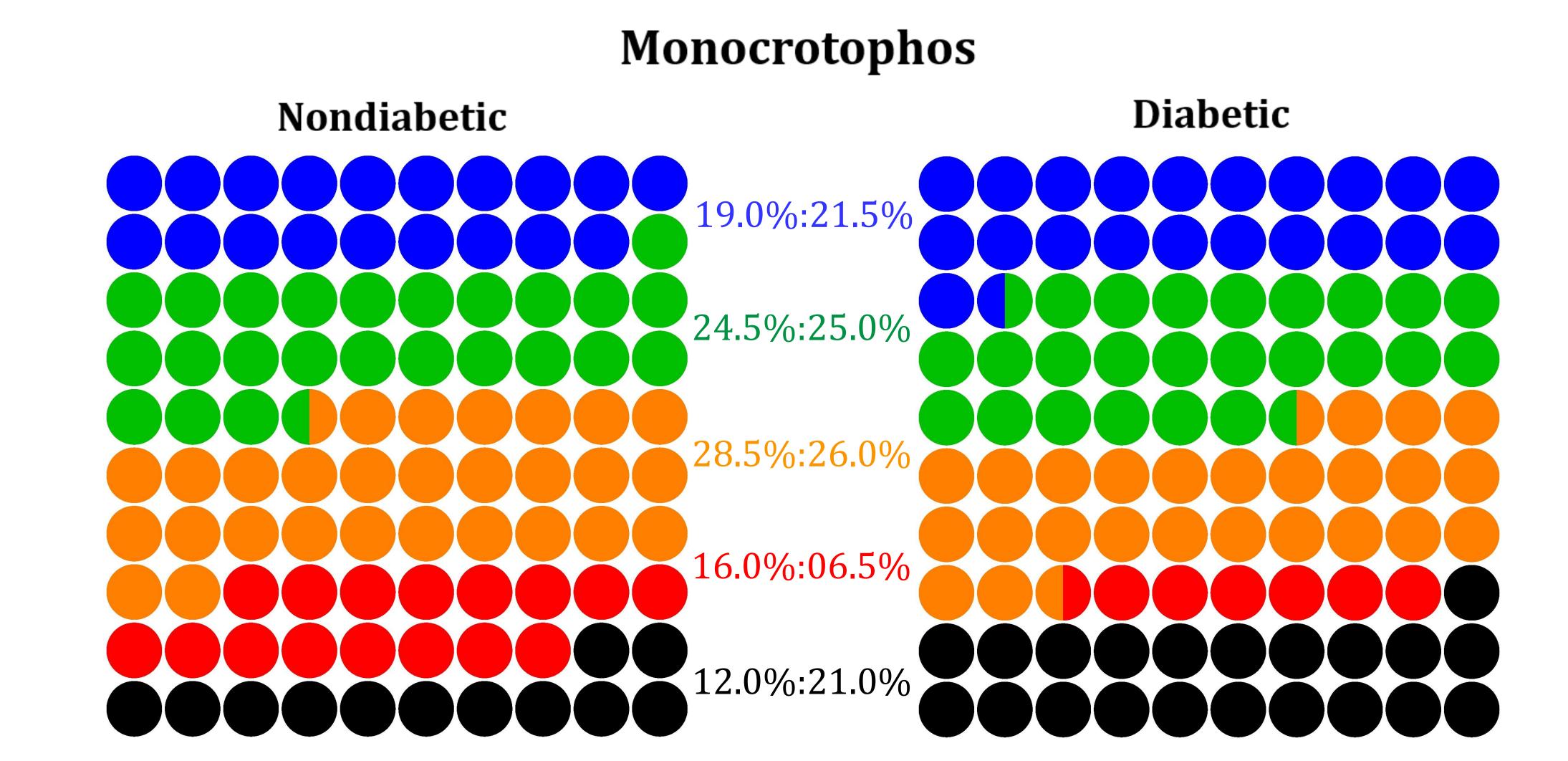
Figure S3| Validation of organophosphate exposure between diabetic (N=554) and nondiabetic (N=248) individuals **a.** Plasma acetylcholine esterase activity of diabetic and nondiabetic individuals. Horizontal dotted lines represents the reference values for males (green) and females (pink). **b.** Plasma MCP, CHL, MAL and MPAR residues. Horizontal lines represent mean; error bars represent s.e.m; \*\*P<0.01, \*P<0.05 Rank sum, Mann-Whitney U Test.



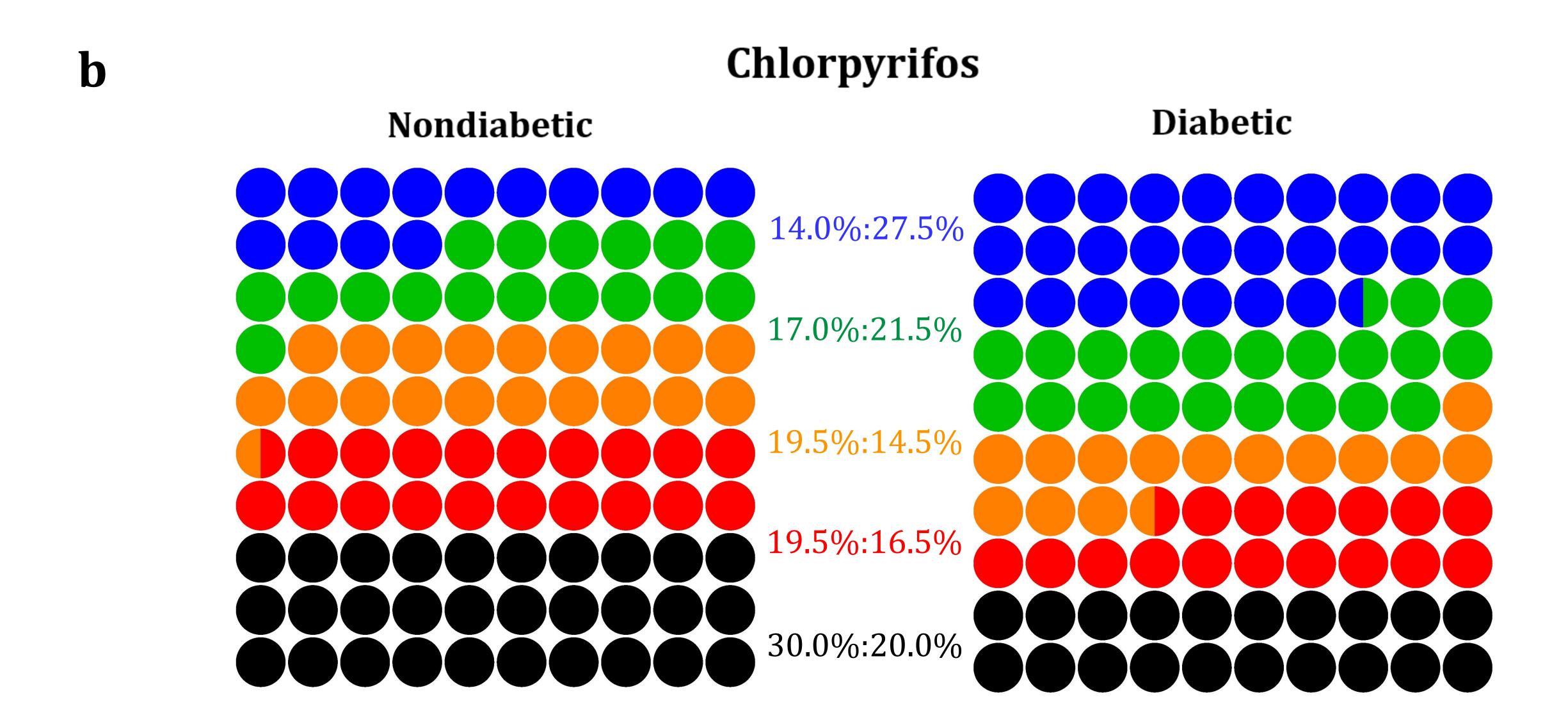
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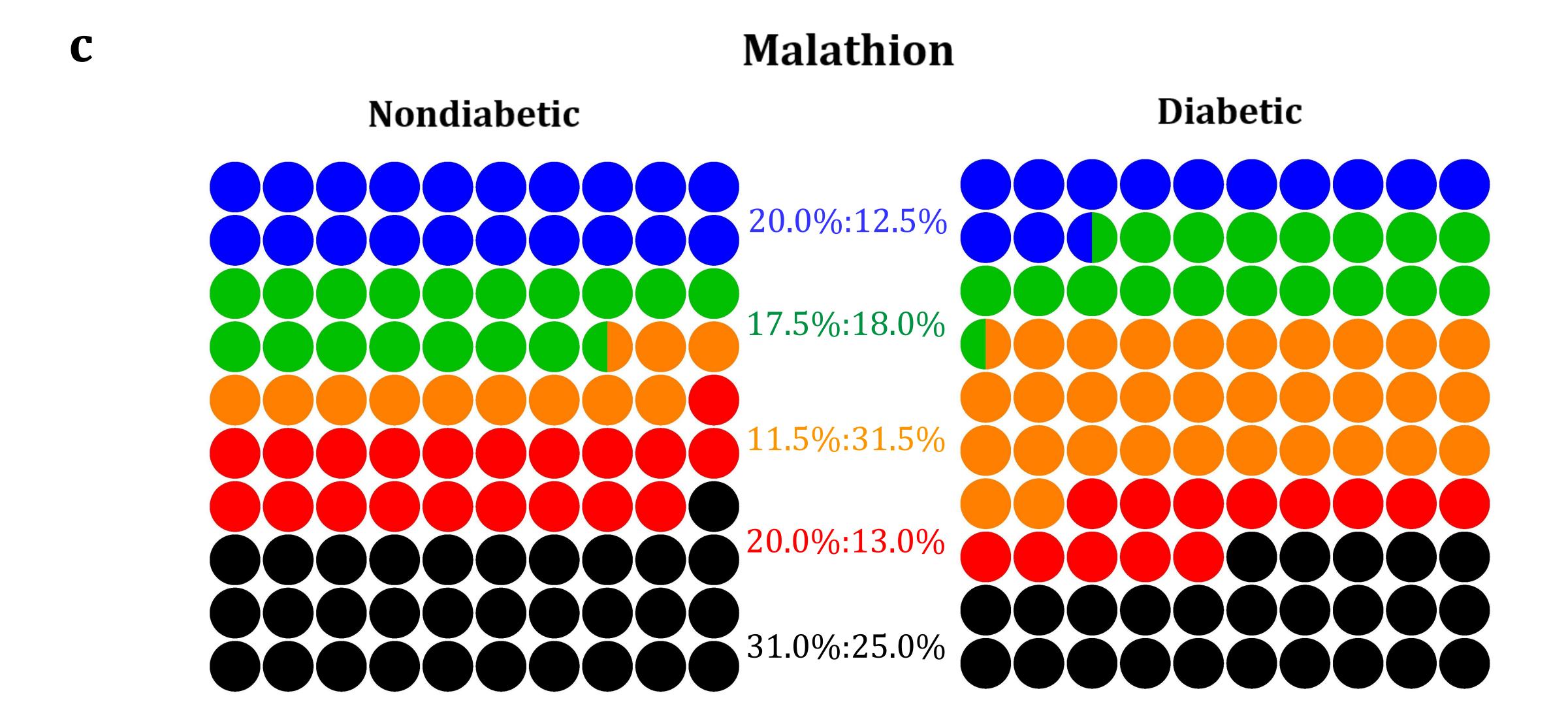
Peak No.	Insecticide	Retention Time (Minutes)	m/z fragments for SIM Mode
1	Monocrotophos	8.20	67,97,109,127,192
2	Methyl parathion	10.31	79,109,125,263
3	Malathion	10.96	93,127,173,285
4	Chlorpyrifos	11.11	97,197,286,314

**Figure S4** | **Gas chromatography** / **Mass spectrometry analysis of organophosphate residues. a.** Gas chromatogram for the four OP standards. **b.** Retention time and mass fragments monitored for the detection of each OP under single ion monitoring mode (SIM).



a





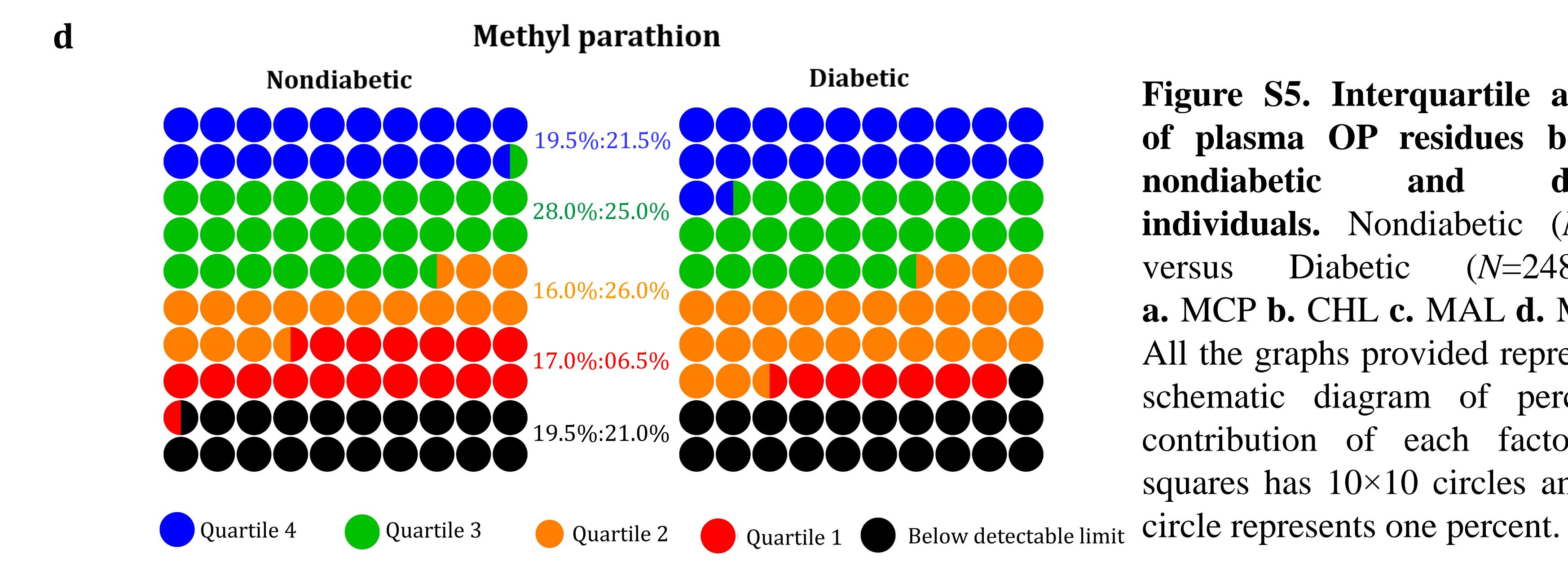
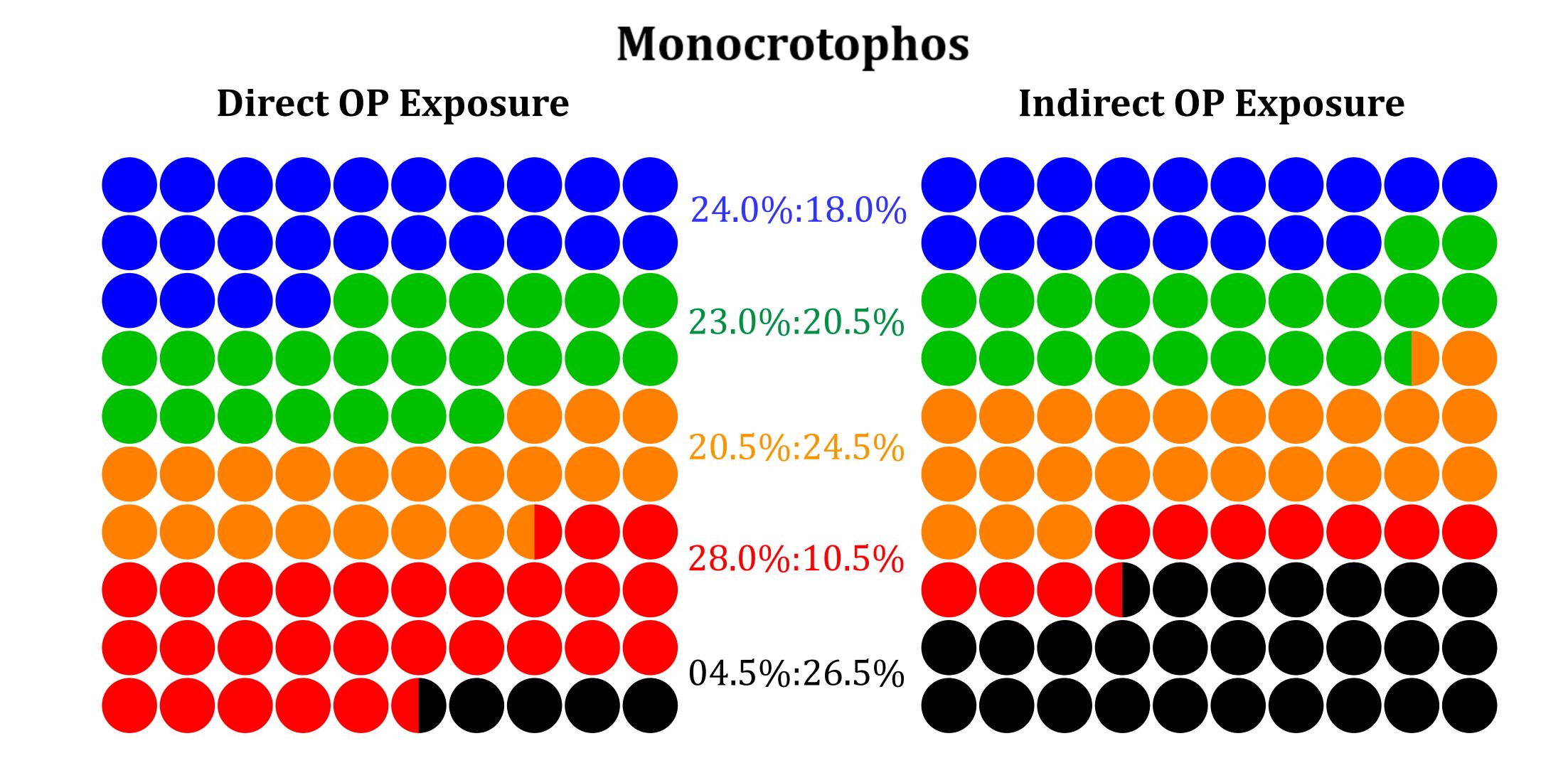
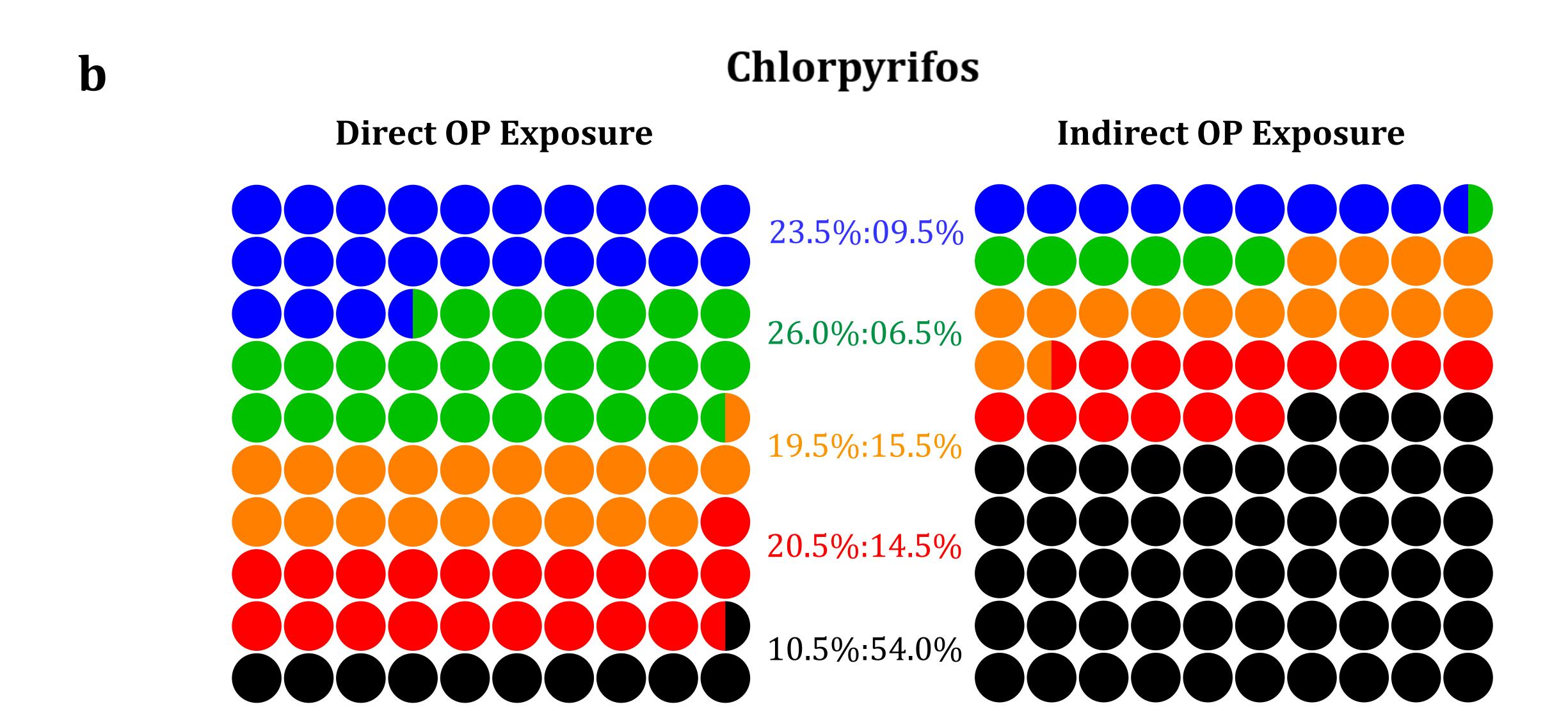


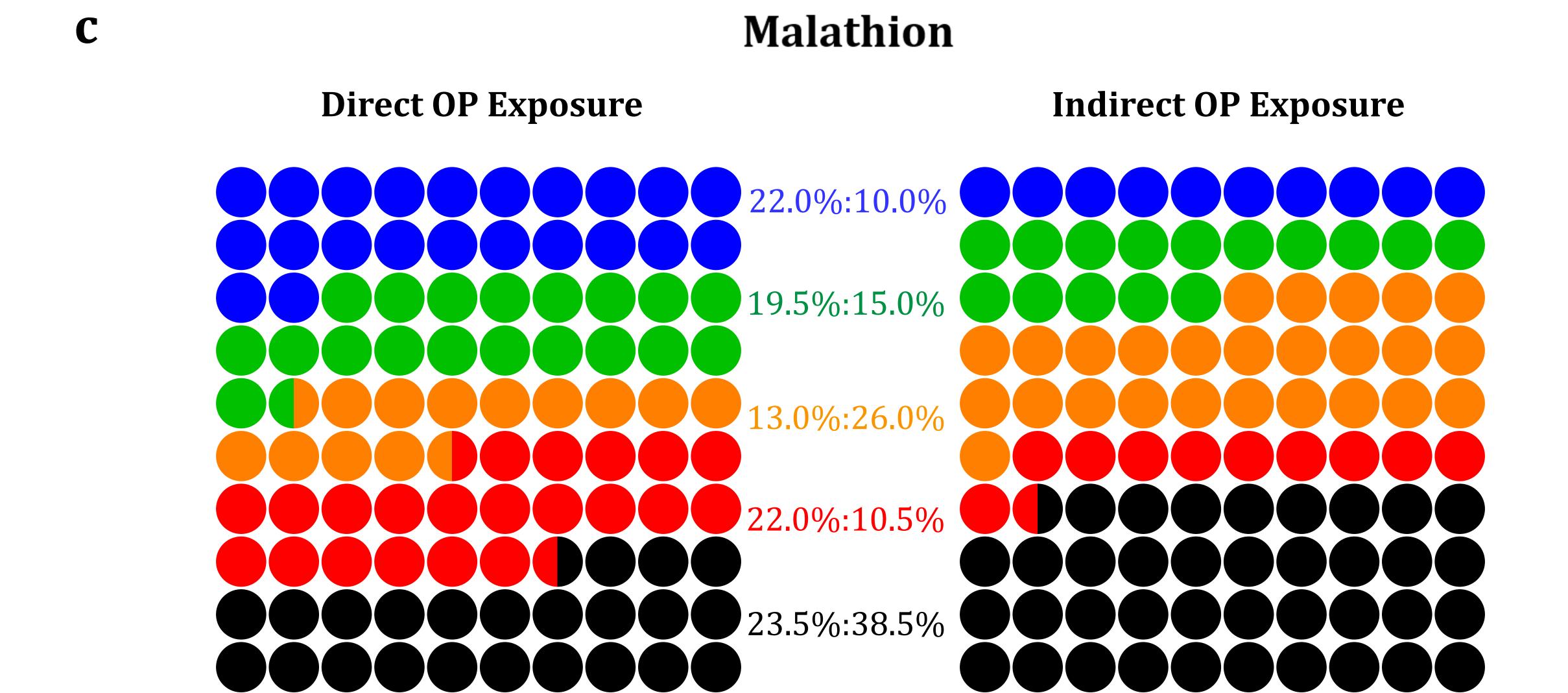
Figure S5. Interquartile analysis of plasma OP residues between nondiabetic diabetic and individuals. Nondiabetic (N=554) Diabetic (N=248)versus a. MCP b. CHL c. MAL d. M.PAR. All the graphs provided represents a schematic diagram of percentage contribution of each factor. The squares has 10×10 circles and each



a

d





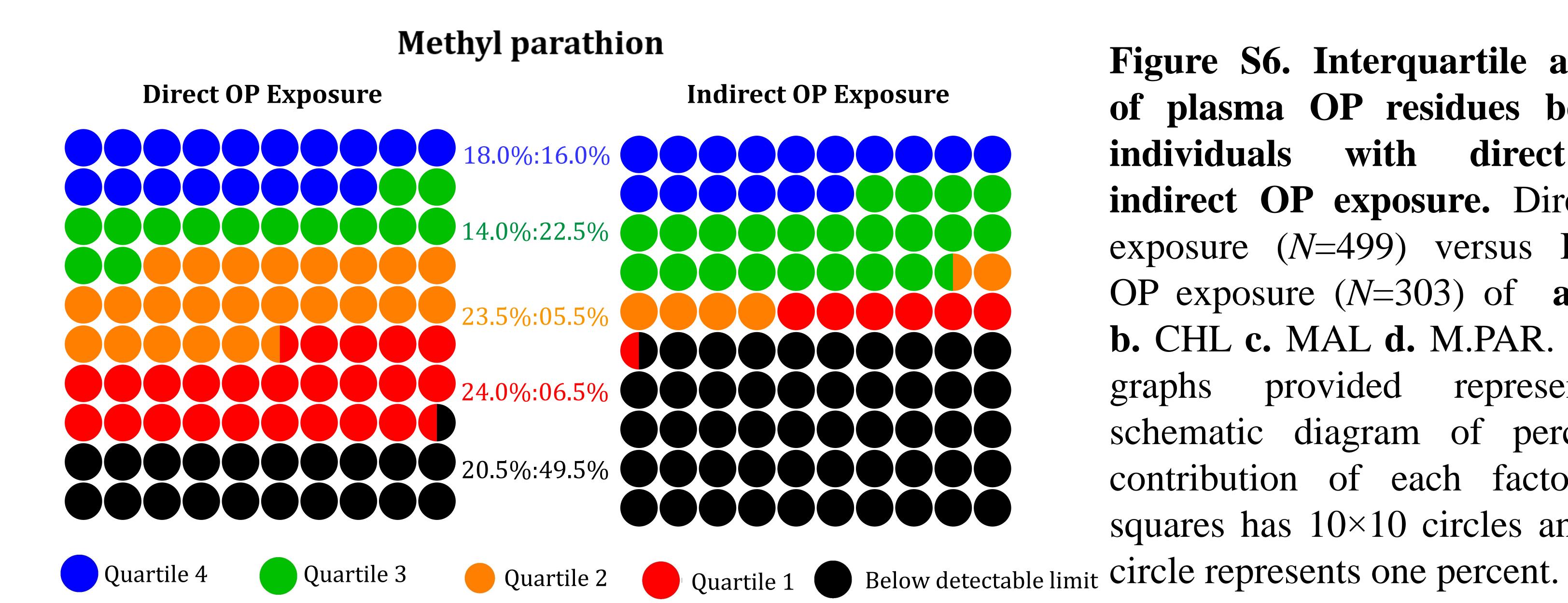


Figure S6. Interquartile analysis of plasma OP residues between individuals with direct and indirect OP exposure. Direct OP exposure (N=499) versus Indirect OP exposure (N=303) of a. MCP b. CHL c. MAL d. M.PAR. All the provided graphs represents a schematic diagram of percentage contribution of each factor. The squares has 10×10 circles and each

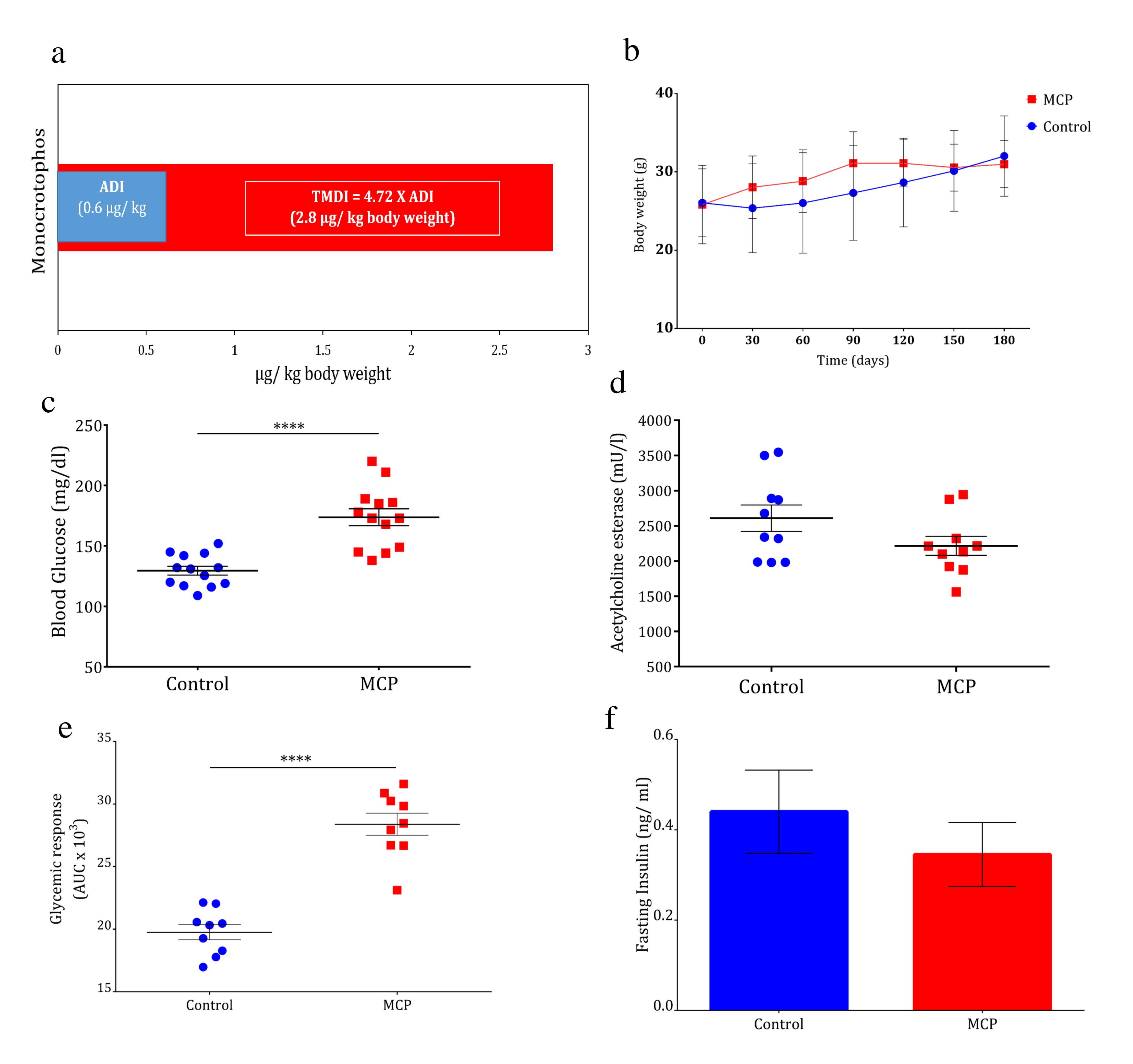
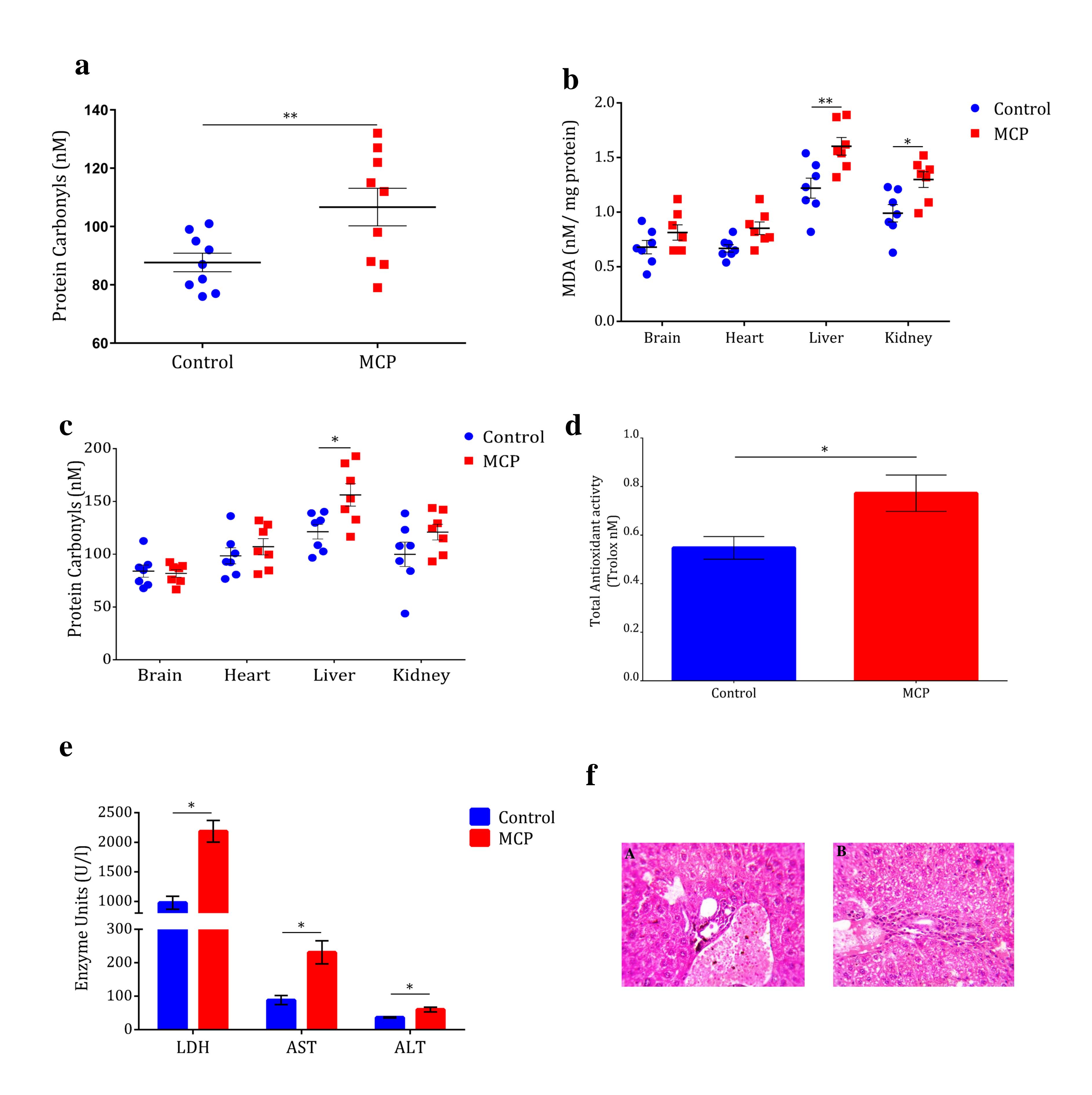
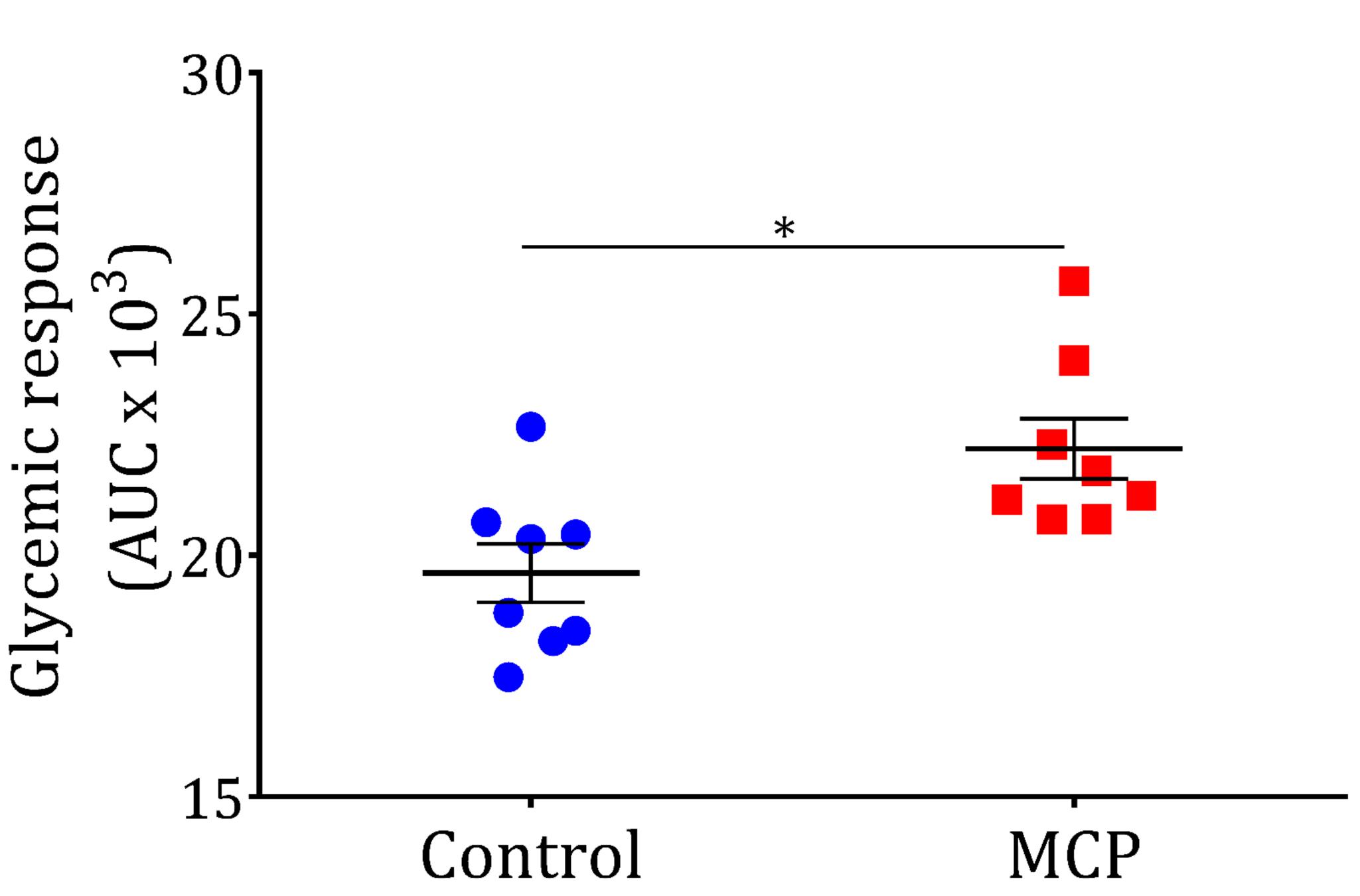


Figure S7 | Chronic organophosphate intake induces glucose intolerance. 8-week old *Balb/c* mice were treated with monocrotophos (MCP) at 10X TMDI dose for 180 days. **a.** Graph showcasing the fold difference between acceptable daily intake (ADI) and theoretical maximum daily intake (TMDI) for MCP. **b.** Periodical body weight control and MCP fed animals (*N*=13). **b.** Fasting blood glucose level of control and MCP group of animals measured after 180 days of treatment (*N*=13). **c.** Acetylcholine esterase (AChE) level of control and MCP fed animals (*N*=13). **d.** Oral glucose tolerance test represented as Glycemic response (AUC) of the mice drinking pure water and MCP mixed water (*N*=09). **e.** Fasting serum insulin levels of mice drinking pure water and MCP mixed water (*N*=04). Symbols (body weight & insulin) or horizontal lines represent means; error bars represent s.e.m. \*\*\*\*P<0.0001, Two-way ANOVA with Bonferroni correction (b) or unpaired two-sided Student *t*-test (c,d,e,f). Experiments were repeated thrice (b,c,d) or twice (e,f).



**Figure S8** | **OP-induced glucose intolerance induces oxidative stress and hepatic damage**. 8-week old *Balb/c* mice were treated with monocrotophos (MCP) at 10X TMDI dose for 180 days. **a.** Protein carbonylation in serum of animals drinking pure water or MCP mixed water (*N*=9) **b.** Lipid peroxidation level in the major organs of control and MCP treated animals (*N*=07). **c.** Level of protein carbonyls in the major organs of control and MCP treated animals (*N*=07). **d.** Total antioxidant activity in the serum of control and MCP fed animals (*N*=04). **e.** Serum levels of hepatic damage markers (LDH, AST & ALT) of control and MCP group of animals measured after 180 days of treatment (*N*=04). **f.** Histopathology (400X) of the liver tissue of control (A) and MCP treated animals (B). Symbols, bars or horizontal lines represent means; error bars represent s.e.m. \*P<0.05, \*\*P<0.01. Unpaired two-sided Student *t*-test. Experiments were repeated twice.



**Figure S9** | **Gut microbiota mediates OP-induced glucose intolerance**. **a.** Schematic representation of faecal transplantation experiment. Faecal samples were collected. from control and MCP fed animals for 180 days and transplanted to randomly selected animals for seven days. **b.** Glycemic response of the animals transplanted with faeces from control and MCP treated animals (N=8). Horizontal lines represent means; error bars represent s.e.m. \*P <0.05, Unpaired two-sided student t-test. Experiments were repeated twice.

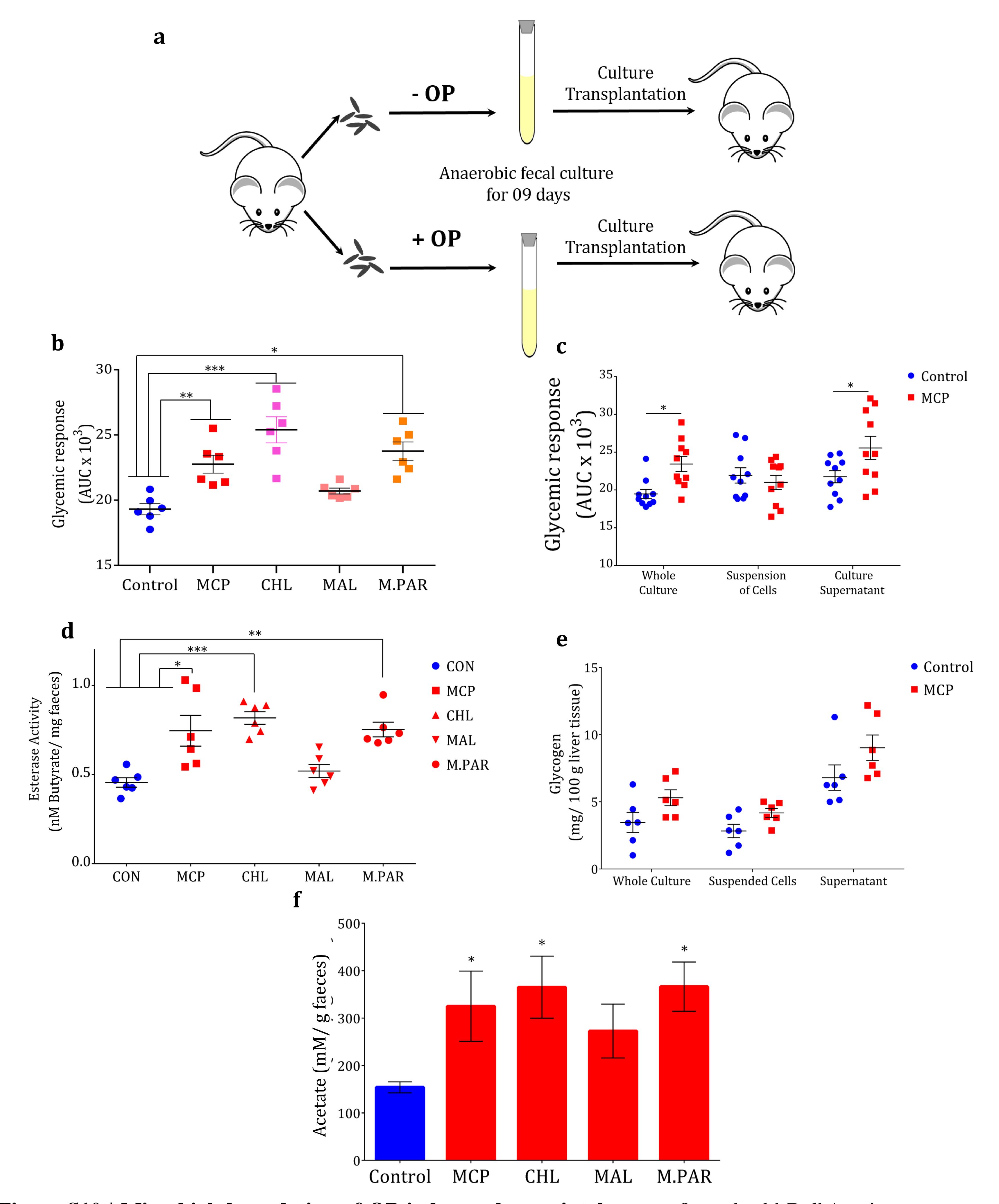
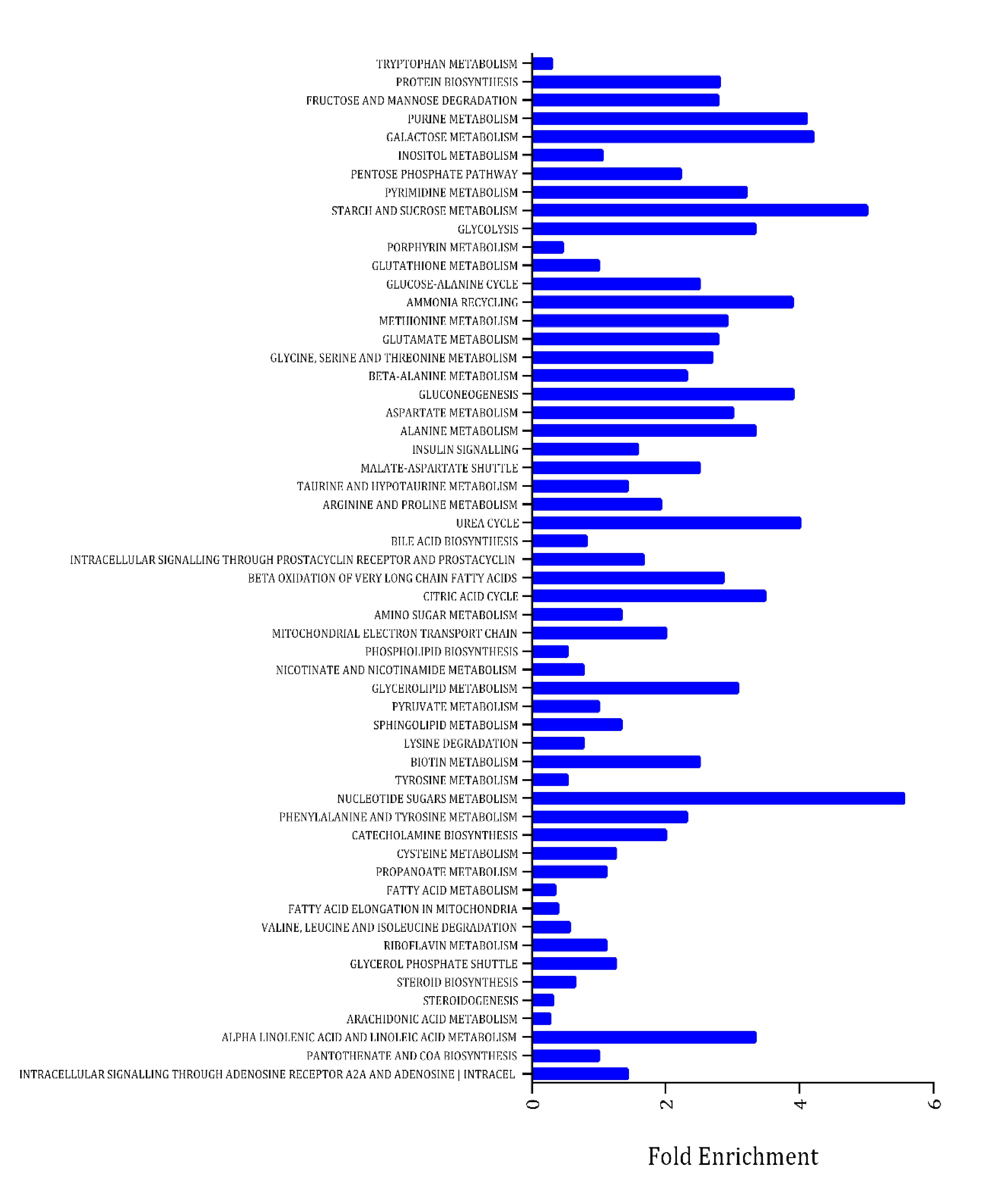


Figure S10 | Microbial degradation of OP-induces glucose intolerance. 8-week old Balb/c mice were treated with faecal cultures grown in presence or absence of OP. a. Schematic representation of culture transplantation experiment. b. Oral glucose tolerance test represented as glycemic response (AUC ×  $10^3$ ) of the animals fed with faecal cultures (N=6). c. Glycemic response of the animals fed with whole culture, suspended cells or supernatant of MCP culture (N=10). d. faecal esterase activity of the animals fed with faecal cultures of different OP (N=06). f. Faecal acetate level of the animals fed with faecal cultures of different OP (N=03). Horizontal lines or bars represent means; error bars represent s.e.m. \*\*\*\*P<0.001, \*\*P<0.001, \*\*P<0.01, \*\*P<0.001. One-way ANOVA with Tukey post-hoc analysis (b,d,f) or unpaired two-sided Student t-test (c,e). Experiments were repeated twice.



**Figure S11** | **Quantitative Metabolite Set Enrichment Analysis.** Enriched pathways analyzed by MetaboAnalyst based on the quantitative metabolite set enrichment analysis of whole metabolite profiling of cecum tissues (*N*=03).

1,2,4-benzenetriol	ethanolamine	lysine	sucrose
1-hexadecanol	fructose	maleimide	taurine
1-monostearin	fructose 1 phosphate	malic acid	threonic acid
2-5-diketopiperazine	fructose-6-phosphate	malonic acid	threonine
2-hydroxybutanoic	fumaric acid	maltose	thymidine
acid	galactonic acid	maltotriose	thymine
2-hydroxyglutaric acid	galactose-6-phosphate	mannose	tocopherol alpha
2-hydroxyvaleric acid	galacturonic acid	mannose-6-phosphate	tryptophan
2-ketobutyric acid	gamma-glutamyl-	methanolphosphate	tyrosine
2-oxogluconic acid	valine	methionine	UDP GlcNAc
2-phenylpropanol	gluconic acid	methylhexadecanoic	UDP-glucuronic acid
3,6-anhydrogalactose	gluconic acid lactone	acid	uracil
3-hydroxybutanoic	glucose	myristic acid	uric acid
acid	glucose-1-phosphate	N-acetylaspartic acid	valine
3-phosphoglycerate	glucose-6-phosphate	N-Acetyl-D-hexosamine	xanthine
5b-cholestanol	glucuronic acid	N-carbamoylaspartate	xylitol
acetophenone	glutamate	N-methylalanine	xylose
adenosine	glutamic acid	nonadecanoic acid	
adipic acid	glutamine	octadecanol	
alanine	glycerol	oleic acid	4.0 1 0.04
aminomalonic acid	glycerol-3-galactoside	ornithine	
arabitol	glycine	orotic acid	Fold Change (MCP treated/ Control)
arachidic acid	glycolic acid	oxoproline	(MCP treated) Control
ascorbic acid	guanosine	palmitic acid	
asparagine	heptadecanoic acid	palmitoleic acid	
aspartic acid	hexuronic acid	pantothenic acid	
behenic acid	homoserine	pelargonic acid	
benzoic acid	hydroxylamine	pentadecanoic acid	
beta-	icosenoic acid	phenol	
glycerolphosphate	indole-3-acetate	phenylacetic acid	
butyrolactam	inosine	phenylalanine	
capric acid	inositol myo-	pimelic acid	
cerotic acid	isoleucine	pinitol	
cholesterol	isolinoleic acid	proline	
cholic acid	isopalmitic acid	pseudo uridine	
citrulline	isothreonic acid	pyrazine2,5-dihydroxy	
conduritol beta expoxide	lactamide	pyrogallol	
creatinine	lactic acid	pyruvic acid	
cysteine	lactobionic acid	saccharic acid	
cysteme cytidine-5-	lathosterol	salicylic acid	
monophosphate	lauric acid	serine	
delta-4-cholestenone	leucine	spermidine	
dihydroabietic acid	lignoceric acid	stearic acid	
erythritol	linoleic acid	succinic acid	

**Figure S12** | **Differential expression of host metabolites.** Heat map elucidating the differential expression in fold change of host metabolites in caecum tissue on chronic exposure to OP (N=03).

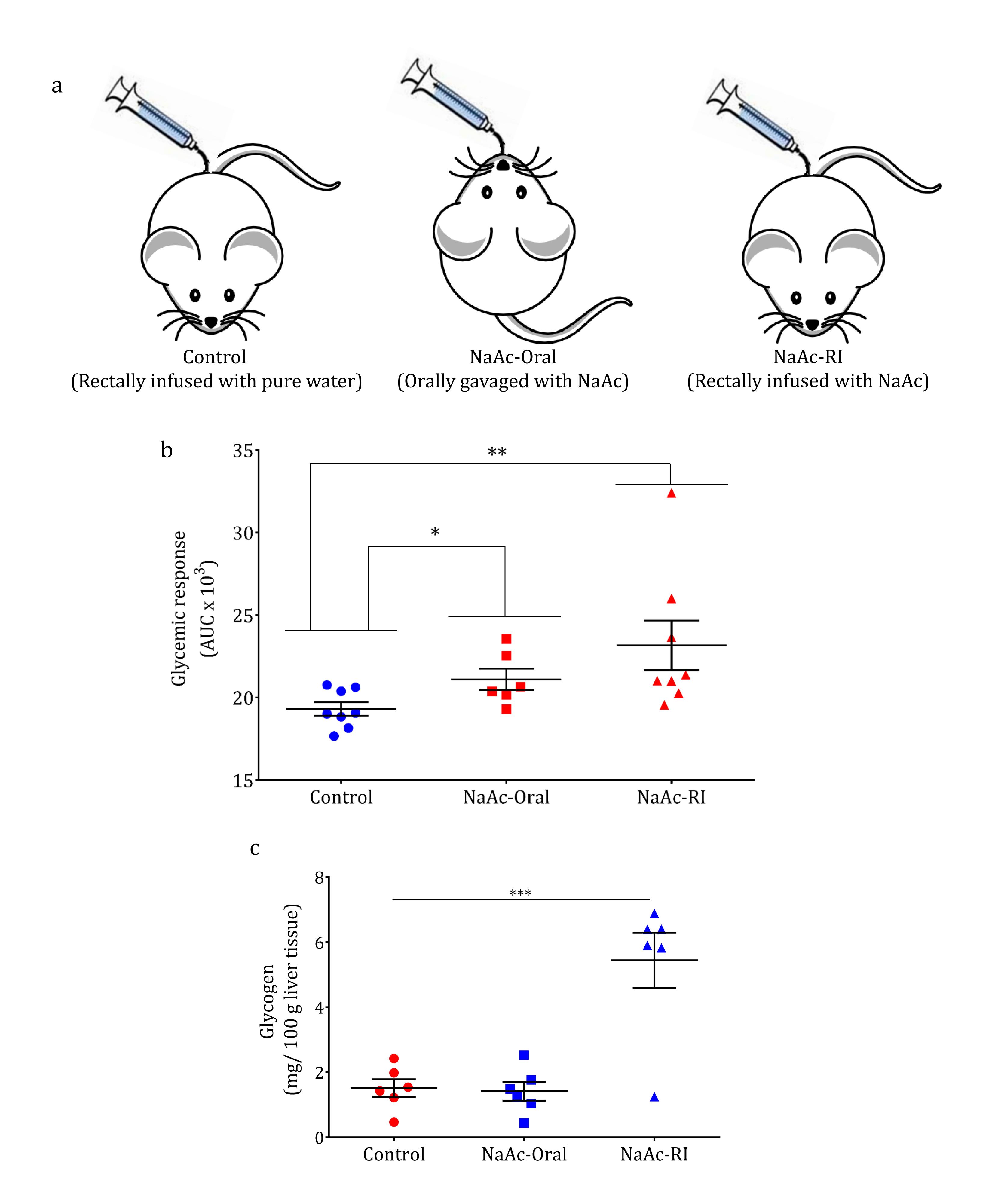
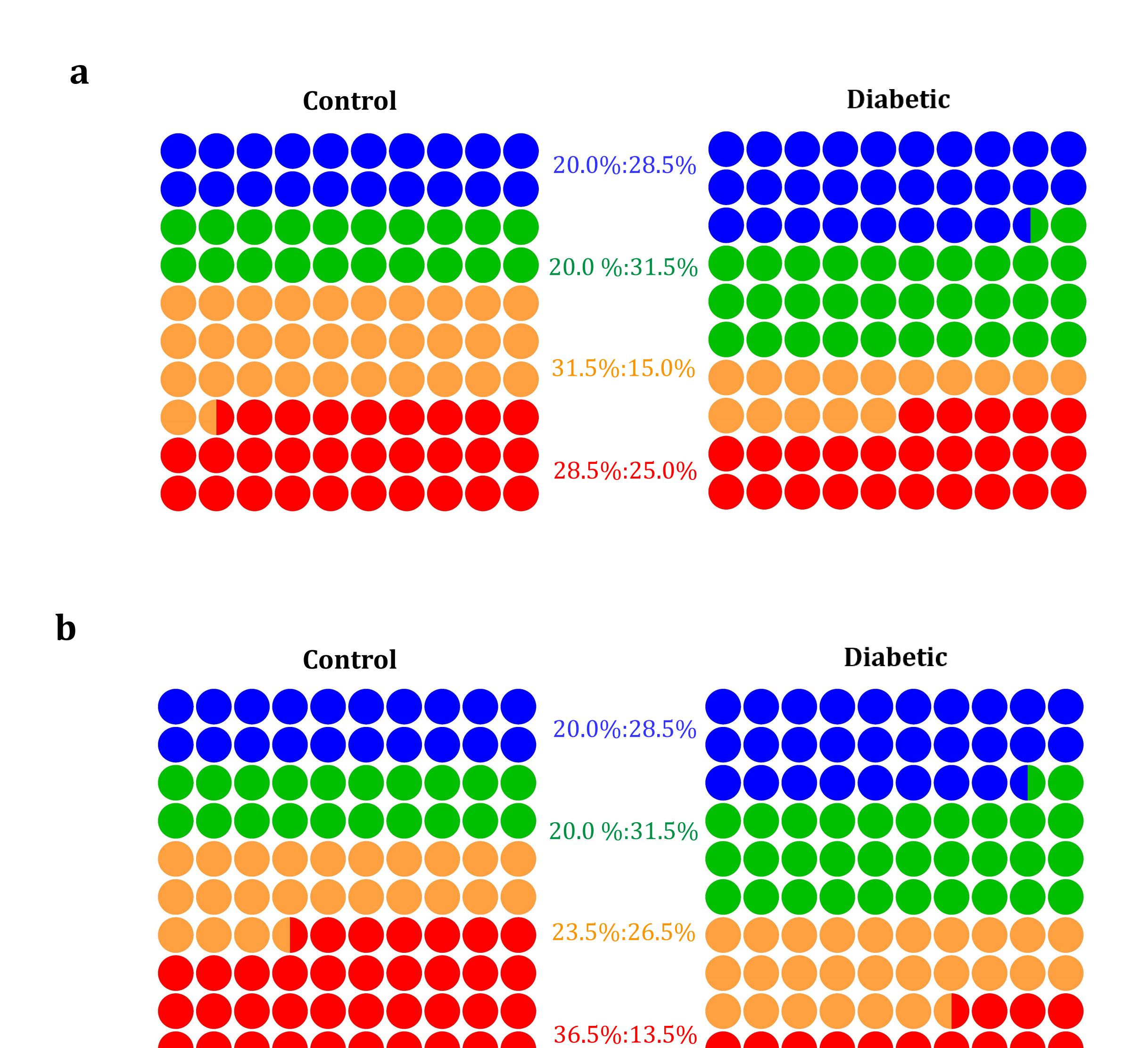


Figure S13 | Rectal infusion of sodium acetate induces glucose intolerance. a. Schematic illustration of oral and rectal infusion of sodium acetate treatment in mice. b. Oral glucose tolerance test represented as glycemic response (AUC  $\times$  10<sup>3</sup>) of animals treated orally and by rectal infusion with sodium acetate (N=08). c. Liver glycogen content of the mice treated orally and by rectal infusion with sodium acetate (N=06). Horizontal lines represent means; error bars represent s.e.m. \*\*\*P<0.001, \*\*P<0.05. One-way ANOVA with Tukey post-hoc analysis. Experiments were repeated twice.



Quartile 3

Quartile 4

Figure S14. Interquartile analysis of faecal parameters between diabetic and diabetic individuals. Control (N=60) versus Diabetic (N=60) of **a.** Faecal esterase activity **b.** Faecal acetate content. All the graphs provided represents a schematic diagram of percentage contribution of each factor. The squares has  $10 \times 10$  circles and each circle represents one percent.

Quartile 2

Quartile 1